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**Guidelines for the use of imaging in the management of patients with myeloma.**

**A British Society for Haematology Guideline**

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DRAFT

## Abstract

The role of imaging in myeloma has gained increasing importance over the past few years. The recently revised definition of myeloma from the International Myeloma Working Group (IMWG) includes cross sectional imaging as a method to define bone disease and incorporates the use of cross sectional imaging in the disease definition for patients with suspected smouldering myeloma. The NICE myeloma guidelines also recommend cross sectional imaging for patients with suspected myeloma. There is also increasing use of imaging in disease assessments and the International Myeloma Working Group has recently incorporated imaging in defining new response categories of minimal residual disease negativity, with or without imaging-based evidence of disease.

Plain X-rays have previously been the standard imaging modality included in a myeloma work up at presentation but evidence is mounting for use of cross-sectional modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and <sup>18</sup>fluoro-deoxyglucose (<sup>18</sup>F-FDG) positron emission tomography (PET)/CT. Funding and therefore availability of newer imaging techniques remains a barrier. Here, we propose an evidence based approach to the use and technical application of the latest imaging modalities at diagnosis and in the follow-up of patients with myeloma and plasmacytoma.

## Methodology

The guideline was compiled according to the BSH process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of

recommendations. The GRADE criteria can be found at the website <http://www.gradeworkinggroup.org>.

## Literature Review

The literature search entailed a systematic search of MEDLINE and PUBMED for publications that included an abstract and were published in English between 1980 to 2015 using the following key words: myeloma, plasmacytoma, imaging, CT, PET, MRI.

## Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemato-Oncology Task Force, Myeloma UK, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH.

## Introduction

Myeloma is a haematological malignancy that is characterised by the clonal proliferation of plasma cells and is commonly associated with bone disease. Typically myeloma presents as multiple focal lesions or a diffuse infiltrate throughout the bone marrow or both and occasionally with extramedullary disease. Myeloma is preceded by a premalignant asymptomatic stage known as monoclonal gammopathy of undetermined significance (MGUS) (Landgren et al, 2009; Weiss et al, 2009). Smouldering myeloma is an intervening phase between MGUS and myeloma but is not a single entity; there is a biological spectrum ranging from a stable state resembling MGUS, which does not progress, to a condition where progression to symptomatic disease is inevitable.

One of the defining criteria for multiple myeloma is the unequivocal presence of

myeloma bone disease (Dimopoulos et al, 2011; Kyle et al, 2009). The new International Myeloma Working Group (IMWG) definition of myeloma incorporates cross sectional imaging and now includes patients with more than one unequivocal focal bone lesion as a defining myeloma-related event indicating the need for treatment (Rajkumar et al, 2014). Cross sectional imaging has also been incorporated into disease assessment in the recently revised IMWG consensus criteria for response assessment (Kumar et al, 2016) and is likely to be increasingly used for disease assessment in clinical trials. This guideline reviews the evidence available for the role of imaging techniques in multiple myeloma, diagnosis, management of vertebral collapse, evaluation of treatment response and evaluation at relapse; the role of imaging techniques in the assessment of plasmacytomas is similarly considered. In addition we provide guidance where possible on the technical considerations around image acquisition and reporting.

## **Use of imaging for diagnosis**

### *Skeletal survey*

A full skeletal survey has for many years been the standard for assessing the presence of myeloma bone disease for any patient with suspected myeloma. Approximately 80% of multiple myeloma patients will have radiological evidence of skeletal involvement using plain radiography (vertebrae in 66% of patients, ribs in 45%, skull in 40%, shoulder in 40%, pelvis in 30% and long bones in 25%) (Collins, 1998). Sites distal to the elbows and knees are rarely affected (Healy and Armstrong, 1998). A clear association exists between the extent of disease on the

skeletal survey in terms of the number of lytic lesions at presentation and tumour load at diagnosis (Durie and Salmon, 1975). Their presence represents a criterion that defines treatment-requiring myeloma even in the absence of symptoms (IMWG, 2003; Kyle & Rajkumar 2009; Bird et al, 2011). The skeletal survey is widely available at a relatively low cost, is simple to use and interpret, allows large areas of the skeleton to be visualised and only exposes patients to relatively low doses of radiation. Careful documentation of the extent of myeloma bone disease is important to provide a baseline for future monitoring.

The major disadvantage of plain X-rays is the significantly lower sensitivity compared to advanced imaging. Lytic lesions are only demonstrated when at least 30 - 50% of the trabecular bone has been lost (Snapper and Khan, 1971) and around 20% of myeloma patients have no abnormal findings by plain X-ray. Plain X-rays cannot distinguish osteopenia or vertebral collapse caused by myeloma from more common causes such as early osteoporosis or corticosteroid use.

A recent systematic review by Regelink et al (2013) confirmed that computed tomography (CT) and magnetic resonance imaging (MRI) are significantly superior to plain X-ray for the detection of skeletal lesions, apart from those of the ribs and skull (Regelink et al, 2013).

Skeletal surveys can be difficult to tolerate for patients with pain and poor mobility due to the duration of the assessment and the need to adopt various positions (D'Sa et al, 2007; Dimopoulos et al, 2009).

Method:

If being done as part of the staging procedure of newly diagnosed myeloma, the skeletal survey should include:

- Postero-anterior (PA) view of the chest
- Antero-posterior (AP) and lateral views of the whole spine, humera and femora
- Lateral views of the skull
- AP view of the pelvis
- Views of any symptomatic areas.

The dose will vary depending on patient size and equipment used, typically 1.5-2.5mSv for an average 70 kg patient.

Skeletal survey has widespread availability and is well established as an assessment tool in myeloma, but has poor sensitivity and should be superseded by low- dose CT scan, PET-CT and WB-MRI. Issues remain relating to lack of capacity and health economic consequences, but performing both a skeletal survey and cross sectional imaging will be the least cost effective approach.

### *Computed tomography*

CT offers improved sensitivity over plain X-rays in detecting lytic lesions and high resolution three-dimensional images generated by CT provide a more detailed evaluation of the bone. Small lytic lesions (<5 mm) that would otherwise be missed by X-ray imaging are detectable by CT, especially in the vertebrae (Mahnken, et al, 2002; Hur et al, 2007). Therefore, bone changes can be identified earlier and



1 potential instabilities and fracture risks estimated with greater reliability [Zamagni et  
2 al, 2012; Horger M et al, 2005), particularly in areas where it is difficult to survey by  
3 plain X-ray, e.g. scapulae and sternum. Given the recently revised classification of  
4 multiple myeloma, CT scanning is a suitable option for patients with suspected  
5 smouldering myeloma, but is not necessary in straightforward MGUS patients,  
6 unless they have skeletal symptoms.

7 From a practical point of view, CT has the advantage of being quick to perform and  
8 allows patients to lie on their back, without the need to change position. CT is also  
9 helpful for visualising soft tissue involvement, assessing spinal fracture stability,  
10 depicting spinal cord and cauda equina compression (although MRI is superior for  
11 this), guiding needle biopsies and surgical interventions and planning radiotherapy.  
12 Despite a number of advantages, conventional CT uses higher doses of radiation (20  
13 mSv for CT of the neck, chest, abdomen and pelvis) than skeletal survey (1.5-2.5  
14 mSv). This has led to the introduction of whole-body low-dose CT (WBLDCT) which  
15 uses a lower tube voltage (kV) and current (mAS) to reduce the energy delivered to  
16 the patient to an effective dose of approximately 4 – 7 mSv. Dose reduction comes  
17 at a cost of reduced image resolution, but this can be partly offset by new iterative  
18 reconstruction techniques so that WBLDCT can now be performed at a similar dose  
19 to skeletal survey. WBLDCT is recommended as first line novel imaging investigation  
20 in European Myeloma Network guidelines (Terpos et al 2015). Studies have shown  
21 that low dose CT accurately assesses the extent of bone destruction and remains  
22 more sensitive than plain X-rays. In one study, the level of confidence in 48  
23 ambiguous plain X-ray findings was raised when WBLDCT from skull base to knees  
24 was used, increasing the detection of osteolytic lesions in the spine seven-fold  
25 (Kropil et al, 2008), whilst in another it could accurately exclude findings in MGUS

1 patients being related to myeloma bone disease (Spira et al, 2012). Studies have  
2 shown WBLDCT outperforms radiographs even in traditionally difficult to assess  
3 areas such as skull and ribs (Princewill et al, 2013). Modern scanners routinely use  
4 1mm resolution which reduces partial volume artefacts which previously hindered  
5 evaluation of ribs. New post processing software shows promise such as the ability  
6 to review unfolded ribs (Bier et al, 2016 Homann et al, 2015) and the skull (Ringl et  
7 al/ 2016) although this is not in routine practise. Dual energy CT is a further  
8 development in which the calcium containing bony structures can be mathematically  
9 subtracted to reveal medullary lesions. Thomas et al (2015) have shown increased  
10 detection of non osteolytic myeloma bone lesions in a series of 32 patients although  
11 found it less sensitive than MRI. Current IMWG guidelines require demonstration of  
12 an osteolytic lesion so this technique is not currently recommended.

13 WBLDCT is capable of demonstrating extramedullary disease (Surov et al, 2014)  
14 and correlates with whole-body MRI findings (Wolf et al, 2014). As well as  
15 extramedullary myeloma, WBLDCT demonstrates clinically significant non osseous  
16 incidental findings (NOIF) such as occult carcinoma and infection so careful extra  
17 skeletal review is mandated. Surov et al retrospectively reported an average of 3.2  
18 NOIF per patient which were clinically significant in 36.6% of 93 patients with  
19 myeloma undergoing WBLDCT (Surov et al, 2014)

21 Other limitations of CT must also be recognised: For example, it may underestimate  
22 bone marrow disease, particularly if it is diffuse, and cortical bone damage with a  
23 homogeneous appearance may be mistaken for osteoporosis or osteopenia (Horger  
24 et al, 2007; Mahnken et al 2002). Furthermore, traditionally CT has not been used to  
25 measure treatment response or provide prognostic information (Durie, 2006).

1 However, recently simplified new CT response monitoring criteria have been  
2 proposed. Changes in measurement of 2-4 medullary lesions in the limbs have been  
3 shown to correlate to change in lytic lesions and haematological indices in a series of  
4 78 patients (Schabel et al, 2016).

#### 5 6 Method:

7 Low-dose CT as an alternative to skeletal survey should incorporate red marrow in  
8 adults since this includes the predominant sites of disease. Body coverage proposed  
9 in the literature is variable but larger series suggest WBLDCT to include roof of skull  
10 to proximal tibial metaphysis (Ippolito et al, 2013). Low-dose CT algorithms  
11 optimised for attenuation correction on positron emission tomography (PET/CT) are  
12 suitable for WBLDCT and should be optimised locally. Low dose CT is given without  
13 IV contrast. As a guide, diagnostic images can be achieved with parameters such as  
14 120 kV, <100 mAs, dose modulation, and iterative reconstruction.

#### 15 16 Recommendations:

- 17 • WBLDCT (roof of skull to proximal tibial metaphyses) is an alternative to  
18 skeletal survey where facilities exist. It is a more sensitive technique for initial  
19 screening for lytic lesions in myeloma than skeletal survey but less sensitive  
20 than MRI at detection of medullary infiltration (1C)
- 21 • WBLDCT is superior to skeletal survey but less sensitive than MRI for the  
22 detection of medullary infiltration and should be considered in asymptomatic  
23 patients with either 10–60% plasma cells on their trephine biopsy or bone  
24 marrow aspirate or an M-protein of > 30 g/L as the detection of more than one

definite focal lesions is diagnostic of multiple myeloma and an indication for treatment (1B)

- WBLDCT is recommended, if MRI is not feasible, for assessing disease in patients with suspected myeloma who remain symptomatic despite having no evidence of osteolysis on the skeletal survey, or to clarify the significance of ambiguous plain radiographic findings, such as vertebral compression fracture or equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain X-rays, such as sternum and scapulae, or to delineate the nature and extent of soft tissue disease. WBLDCT is, however, less sensitive than whole body MRI for assessing medullary infiltration (1C)

### *Magnetic resonance imaging*

MRI has emerged as a valuable imaging modality in myeloma because of its ability to directly visualise the disease within the bone marrow rather than its secondary effects on cortical bone. It is the most sensitive tool available for detecting marrow infiltration at an early stage, before bone destruction occurs, as well as offering improved detection of lesions, particularly in the axial skeleton (Dimopoulos et al, 2015). Several studies have compared MRI (limited or whole body) to skeletal survey at diagnosis (see Table 1) and have shown that MRI may detect up to 50% more lesions, although the skeletal survey continues to outperform it at certain sites e.g. ribs (Walker et al, 2007). Comparison of MRI with CT also indicates that MRI outperforms CT (Bauer-Melnyk et al 2008, Laroche et al 1996) with a pooled sensitivity of 91% [95% CI: 88 to 94%] and pooled specificity of 41% [95% CI: 26 to 58%] for MRI in a recent systematic review (Regelink et al, 2013).

1 MRI is useful for confirming a diagnosis of solitary plasmacytoma, by ruling out  
2 additional disease (Dimopoulos et al, 2000; Moulopoulos et al, 1993; Liebross et al,  
3 1998), for detecting lesions in symptomatic patients with myeloma whose skeletal  
4 surveys are normal, for assessing disease burden in patients diagnosed with  
5 nonsecretory or oligosecretory myeloma, and for evaluation of extramedullary  
6 disease (Dimopoulos et al, 2011). It is the technique of choice for suspected spinal  
7 cord compression (Joffe et al, 1988).

8 MRI provides greater contrast resolution than CT and has the advantage that it does  
9 not expose patients to radiation. Established MRI protocols include T1-weighted  
10 turbo spin echo, T2-weighted turbo spin echo and short tau inversion recovery  
11 (STIR) sequences. T1- and T2-weighted signal intensity provides the ratio between  
12 cellular and fatty components in the bone marrow, and in myeloma the increased  
13 cellular and decreased fatty components give rise to a hypointense signal on T1-  
14 weighted images, and a hyperintense signal T2-weighted images and STIR  
15 sequences. On the whole, published studies have utilised whole body techniques  
16 with STIR and T1 sequences. MRI limited to the spine and pelvis may be performed,  
17 but optimal methods need to be defined for evaluation of the skull and for  
18 determining the preferred extent of coverage of the appendicular skeleton (as  
19 approximately 10% of patients present with extra-axial disease only) (Bauerle et al,  
20 2009).

21  
22 MRI can demonstrate patterns of bone marrow involvement which are generally  
23 described as normal, focal, diffuse (homogeneous or heterogeneous), variegated  
24 (also known as salt and pepper), or a combination of these. Normal or variegated  
25 marrow patterns have been associated with lower disease burden, whereas focal or

diffuse marrow patterns have been associated with higher disease burden (Bauer-Melynk et al, 2005). A focal or diffuse pattern of bone marrow involvement is not unique to myeloma and may be present in other haematological malignancies and in metastatic disease (Vogler et al, 1988).

MRI has prognostic value. One study showed that patients with more than seven focal lesions on initial spinal MRI and cytogenetic abnormalities had a poorer five-year overall survival than patients without these features (37% versus 76%) (Walker et al, 2007). The presence of at least one focal lesion or the presence of a diffuse infiltration pattern on whole body MRI is related to a higher risk of progression of patients previously labelled as having asymptomatic disease (Hillengass et al, 2010). The two-year progression rate for such patients with  $\leq 1$  focal lesion was 20% compared to 70% for patients with  $> 1$  focal lesion (Hillengass et al, 2010), and patients with lesions required systemic treatment at an earlier time point than patients without lesions (16 months versus 46 months) (Hillengass et al, 2014), similarly to the Greek study group (median 15 months,  $P=0.001$ ) (Kastritis et al, 2013). The IMWG revised classification is currently restricted to focal involvement where a lesion of diameter  $> 5\text{mm}$  is regarded as positive; any equivocal lesions should be imaged again after three to six months. Symptomatic patients with a diffuse pattern of marrow involvement at staging have a poorer outcome (Song et al, 2014; Moulopoulos et al, 2005; Lecouvet et al, 1998; Moulopoulos et al, 2012). Although recognised as a prognostic factor, diffuse marrow involvement was not included as an indication to start treatment in patients with suspected smouldering myeloma and this reflects not only the need for greater evidence but also that assessment of marrow infiltration can be challenging and subjective. False positives

can occur, e.g. following administration of granulocyte-colony stimulating factor, and both focal or diffuse bone marrow patterns may represent other malignant infiltrations, or be caused by a previous bone marrow biopsy (Hanrahan et al, 2010).

Image enhancement with contrast agents such as gadolinium-diethylene triamine pentaacetic acid (DTPA) may not always be possible as these agents should be avoided in patients with renal dysfunction because of the risk of nephrogenic systemic fibrosis (Nicholas et al, 2012). The main limitation of MRI is the long acquisition time (up to one hour) which may be difficult to tolerate for those with severe back pain, or those who suffer from claustrophobia. It is also contraindicated in patients with cardiac pacemakers and metallic prostheses.

At present, there is no evidence to indicate that MRI is necessary for patients with MGUS, although a recent study suggested it might be useful to help identify MGUS and the various stages of myeloma (Kloth et al, 2014].

Newer MRI protocols enable whole-body T1 ± gadolinium contrast agent administration, T2 ± fat saturation and diffusion-weighted sequences to be performed. Quantification of skeletal apparent diffusion co-efficient, vascularity and marrow fat fraction may be possible with diffusion-weighted, dynamic contrast-enhanced and T1 DIXON sequences (Koutoulidis et al, 2017). These sequences capture the physiological changes that may occur with plasma cell infiltration in addition to the morphological changes including a higher signal on high b-value diffusion weighted sequences, a higher apparent diffusion co-efficient compared to normal bone marrow on diffusion-weighted sequences; a higher vascularisation

1 compared to normal bone marrow on contrast enhanced sequences and a lower fat  
2 fraction compared to normal marrow. For example at initial staging diffusion  
3 sequences are highly sensitive to diffuse marrow infiltration in comparison to  
4 standard TSE and STIR sequences. Nevertheless, although these techniques have  
5 the potential to improve the specificity of MRI, good quality whole body MRI evidence  
6 remains limited as to their usefulness at diagnosis; instead they may better serve in  
7 other settings e.g. response monitoring where a change in quantitative parameters  
8 such as apparent diffusion co-efficient may be warranted, until there is further high  
9 quality evidence from multi-centre prospective trials (Messiou et al, 2012; Huang et  
10 al, 2012; Messiou et al, 2015)

#### 12 Method:

13 Whole body MRI (typically from the vertex to knees) is recommended. Increasing  
14 coverage to below knees improves sensitivity but is offset by increased time for the  
15 examination. Whole body MRI should include fast T1- and T2-weighted imaging with  
16 fat suppression (e.g. STIR) in either the axial or coronal plane. With MRI scanners  
17 capable of diffusion-weighted imaging, the acquisition should be performed with at  
18 least two b values (e.g. b 50 and 900 s/mm<sup>2</sup>). An additional T1-weighted sagittal  
19 spine sequence should be incorporated to facilitate assessment of vertebral collapse  
20 and cord compression. Where whole body MRI cannot be performed, STIR and T1-  
21 weighted sagittal spine and axial pelvis sequences should be performed.

#### 22 Recommendation

- 23 • MRI is the gold standard for the detection of bone marrow infiltration by  
24 plasma cells in patients with suspected myeloma (2B).



- MRI has superior detection of lesions compared to skeletal survey and should be considered in asymptomatic patients with either 10–60% plasma cells on a trephine biopsy or bone marrow aspirate or an M-protein of > 30 g/L as the detection of more than one definite focal lesions is diagnostic of multiple myeloma and an indication for treatment (1B).
- MRI is the recommended technique in patients with suspected myeloma who remain symptomatic despite having no evidence of osteolysis on the skeletal survey and to clarify the significance of ambiguous plain radiographic findings, such as vertebral compression fracture or equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain X-rays such as sternum and scapulae and to delineate the nature and extent of soft tissue disease (2C).
- Where whole body MRI is not possible, MRI of the spine and pelvis may be performed but may not detect up to 10% of lesions located in the appendicular skeleton (2C). Where MRI cannot be performed, low-dose whole body CT is an alternative but has lower sensitivity and specificity for marrow infiltration. (2C).

#### *Positron emission tomography/computed tomography (PET/CT)*

PET uses <sup>18</sup>Fluorine-fluoro-deoxy-glucose (<sup>18</sup>F-FDG) as a radiotracer to detect glucose metabolism throughout the body, making use of the fact that tumour cells have a higher metabolic rate than normal cells and, therefore, higher <sup>18</sup>F-FDG uptake. Uptake can be estimated by calculating the standardised uptake value (SUV), which is the uptake of <sup>18</sup>F-FDG corrected for administered dose and patient

weight.

FDG PET imaging has limited spatial resolution but combining it with CT imaging addresses this issue and enables areas of active disease to be identified with exact anatomical localisation (Zamagni et al, 2012; Agarwal et al, 2013; Nakamoto et al, 2014). This type of information is valuable in myeloma and FDG PET/CT has a potential role in initial diagnosis (Walker et al, 2012), particularly in extramedullary disease and non secretory myeloma (Orchard et al, 2002; Dimopoulos et al 2009; Durie et al, 2002; Agarwal et al, 2013).

Several studies have shown that FDG PET/CT identifies more lesions than plain X-rays in 40–60% of cases and can also detect lesions in patients with negative skeletal surveys (Nanni et al, 2006). FDG PET/CT is useful for investigating equivocal cases when skeletal survey has not detected clear evidence of lytic bone damage, but patients remain symptomatic (Dimopoulos et al, 2009). It is also useful for assessing patients with smouldering myeloma and is a recommended imaging technique for evaluating such cases (Rajkumar et al, 2014). There is little evidence for a role for FDG PET/CT in stable MGUS patients who are at low risk of progression to multiple myeloma. Durie et al performed FDG PET/CT scans in a series of 66 patients with myelomatous and monoclonal disease. Fourteen patients had MGUS. All had normal PET/CT scans and only one patient progressed to multiple myeloma after eight months (Durie et al 2002).

The sensitivity of FDG PET/CT in detecting focal lesions in the spine and pelvis is broadly similar to MRI, but the latter is thought to be superior in detecting diffuse and

1 variegated bone marrow infiltration (Breyer et al, 2006; Fonti et al, 2008; Mesguich et  
2 al, 2014). In one study, FDG PET/CT was used to detect bone marrow involvement  
3 at initial diagnosis. Sensitivity for the detection of bone marrow involvement shown  
4 on trephine biopsy was 90% while specificity was 100% but interestingly, a  
5 significant correlation was observed between  $^{18}\text{F}$ -FDG  $\text{SUV}_{\text{max}}$  on PET/CT and bone  
6 marrow cellularity and plasma cell ratios on biopsy samples (Sager et al, 2011). This  
7 led to the suggestion that it may be possible to replace bone marrow biopsy with  
8 FDG PET/CT as a marker of disease extent, but further studies are needed to  
9 confirm this, particularly in patients with nonsecretory myeloma.

10  
11 FDG PET/CT can provide prognostic information in newly diagnosed myeloma  
12 patients. The presence of three or more lesions was shown initially to be an  
13 independent predictor of overall survival (OS) (Bartel et al, 2009) and in a follow up  
14 study of 429 newly diagnosed myeloma patients in the same institution PET was the  
15 only independent predictor of OS (Usmani et al, 2013). In a European study, the  
16 presence of three or more focal lesions at baseline, a  $\text{SUV}_{\text{max}}$  greater than 4.2 and  
17 the presence of extramedullary disease adversely affected both progression-free  
18 survival (PFS) and OS (Zamagni et al, 2011).

19  
20 The level of FDG uptake on PET/CT may predict pathological fractures. A  $\text{SUV}_{\text{max}}$   
21 greater than 3.2 was shown in one study to differentiate between old and new  
22 vertebral fractures, and  $\text{SUV}_{\text{max}}$  greater than 3.5 when combined with MRI showing  
23 vertebral body involvement predicted fracture in 5/7 patients either at the time of  
24 imaging or within 10 weeks of the scan. It should be noted, however, that this  
25 retrospective study was limited by small patient numbers (Mulligan et al, 2011).

Fractures are known to adversely affect survival (Sonmez et al, 2008) so the ability to predict fracture risk with FDG PET/CT is of potential significance, allowing patients to be managed appropriately and possibly improve outcome.

FDG PET/CT must be interpreted with care as it has a high rate of false positives compared to other imaging techniques. False positives can occur in areas of inflammation or infection, as a result of post-surgical or vertebroplasty changes or because of the presence of other malignant conditions. On the other hand, false negatives may occur with concurrent use of corticosteroids and in diabetic patients with raised blood glucose. To overcome these potential problems, other radiotracers such as  $^{11}\text{C}$  methionine and  $^{18}\text{F}$ -fluorodeoxy-L-thymidine ( $^{18}\text{F}$ -FLT) have been investigated (Dankertl et al, 2007) but these are not widely available and more studies are needed to confirm their clinical value in myeloma. Until then,  $^{18}\text{F}$ -FDG remains the radiotracer of choice. The radiation dose is similar to that of conventional whole body CT

Whole body imaging from vertex to toes is recommended using methods published in European guidelines for performing  $^{18}\text{F}$ -FDG tumour imaging (Boellaard et al, 2015). No standardised criteria currently exist for the interpretation of myeloma imaging, but recommendations for PET/CT reporting in myeloma are suggested, based on published experience in the field (Mesguich et al, 2014). Table 2 shows recommendations for myeloma imaging and reporting using PET/CT and Table 3 shows criteria for the interpretation of FDG bone and bone marrow uptake in patients with myeloma.

Further recommendations are anticipated in 2017 from an international working group, involving experts from clinical trials groups and cancer centres, which critically aim to provide standardisation of PET/CT methods.

#### Recommendations:

- FDG PET/CT has superior detection of lesions compared to skeletal survey and should be considered in asymptomatic patients with either 10–60% plasma cells on their trephine biopsy or bone marrow aspirate or an M-protein of > 30 g/L as the detection of more than one definite focal lesions is diagnostic of multiple myeloma and an indication for treatment. (1B)
- FDG PET/CT may be considered for patients with newly diagnosed nonsecretory or oligosecretory myeloma and for evaluation of extramedullary disease. (2C) Although FDG PET/CT has some prognostic value when used in the initial diagnosis of myeloma, there is currently insufficient evidence to justify the routine use of FDG PET/CT in all cases of newly diagnosed myeloma (2C)

#### **Use of imaging in the management of vertebral collapse/spinal cord compression**

Vertebral compression fractures are common in myeloma and affect up to 70% of patients during the course of their disease (Lecouvet et al, 1997). Vertebral collapse causes severe pain and can lead to significant spinal deformity, loss of total body height, impaired mobility, respiratory compromise and gastro-intestinal discomfort. Of greatest concern, however, is the risk of spinal cord compression secondary to

vertebral collapse. Plain X-rays are the initial diagnostic modality to confirm a suspected vertebral fracture, but urgent additional imaging is essential to accurately characterise spinal disease. Importantly, cord compression can be due to soft tissue disease. CT scans can accurately identify unstable vertebrae, at risk of fracture (Horger et al, 2005; Kropil et al, 2008; 51; Touzeau et al, 2013), identify a soft tissue component, provide better images of more complex fractures and help determine the degree of vertebral compression (Alexandru et al, 2012).

MRI is the most sensitive and specific imaging modality to assess spinal lesions (Carlson et al, 1995; Dimopoulous et al, 2015). It enables the morphological detection of vertebral compression fractures and provides an accurate assessment of the level and extent of cord or nerve root compression (Joffe *et al*, 1988; Mouloupoulos *et al*, 1999; Dimopoulos *et al*, 2009). Thus, in the event of suspected cord compression, whole spine MRI including a STIR sequence is the imaging modality of choice (Dimopoulos et al, 2009; Brooks et al, 2014). Additional CT imaging may be required to assess spinal instability more accurately both at diagnosis and in pre-treated patients (particularly as MRI signal intensity and MRI changes may normalise with treatment). The spinal instability neoplastic score (SINS) classification (Fourney *et al*, 2011) is useful for evaluating the stability of the spine at the involved levels. This evidence-based classification helps to determine stability/instability in a spine affected by tumour by taking into account the location in the spine, pain, lytic nature, alignment, percentage vertebral body height loss and the presence of posterior bony elements: a score between 0–6 denotes stability, a score of 7–12 denotes indeterminate (possibly impending) instability and a score of 13–18 signifies instability.

### Recommendation:

- Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients (2B)
- Urgent CT may be used to establish the presence of suspected cord compression in cases where MRI is either unavailable, not suitable due to patient intolerance or contraindicated e.g. intraorbital metallic foreign bodies or cardiac pacemakers (2C)
- Where there is a suggestion of spinal instability on MRI, spinal surgeons may recommend a CT scan with sagittal and coronal reconstructions to assess for vertebral body fracture and any involvement of the pars, facet joints and pedicles. The SINS classification (Fourney *et al*, 2011) is useful for evaluating the stability of the spine at the involved levels (2C)

### **Use of imaging in the assessment of treatment response and disease relapse**

Assessment of treatment response, monitoring during follow-up and detection of disease relapse in myeloma patients is predominantly based on paraprotein and serum free light chain measurement. Imaging is important for reassessing bone disease at suspected relapse in patients with new bony symptoms and in assessing disease in patients with nonsecretory, oligosecretory or extramedullary disease. With modalities that now enable bone marrow infiltration and disease activity to be

measured, imaging has, in fact, the potential to play a wider role in assessing treatment response and disease relapse. The IMWG has recently incorporated imaging into disease response assessment (Kumar *et al*, 2016) and this will lead to imaging being increasingly incorporated into disease assessment in future clinical trials although it is unclear how practical this will be in the UK.

#### *Skeletal survey and CT scan*

Plain X-ray assessment is of limited use in assessing treatment response and in monitoring as lytic bone lesions seldom show evidence of healing on plain X-rays (Wahlin *et al*, 1982). Its role is more restricted to helping define progressive disease by providing evidence of new bone lesions but caution is needed, as new vertebral compression fractures on plain X-rays do not necessarily signify disease progression and may represent structural weakness (Collins, 2005).

Similarly, CT is not felt to be particularly useful for assessing treatment response, or for following up bony lesions but further studies are needed to evaluate its use in this setting. It may be used to demonstrate resolution of extramedullary disease, following treatment and may help for response assessment of medullary involvement at some sites e.g. pelvic bones and appendicular skeleton [Horger *et al*. Cancer 2007].

#### Recommendations:

- There is insufficient evidence of benefit to recommend routine follow up skeletal survey in untreated asymptomatic patients in the absence of signs of



disease progression (1B)

- Any new symptomatic areas of the skeleton should be specifically targeted.

However, if disease progression occurs within three months of the previous skeletal survey, in the absence of new skeletal symptoms, a new skeletal survey is unlikely to provide additional information

(1B)

### *Magnetic resonance imaging*

In the treatment response setting, there is a wide spectrum of treatment-induced changes with conventional MRI.

In some cases, complete resolution of initial marrow abnormalities is observed in patients achieving a complete response, while conversion from diffuse to focal or variegated pattern of infiltration is seen in those achieving a partial response (Moulopoulos et al, 1994). A good response to treatment can also be demonstrated by an increase in focal lesion signal intensity on T2-weighted spin echo images, probably related to necrosis, and the disappearance of contrast-induced rim-enhancement (Bauer-Melnyk et al, 2005). In the post-autologous transplant setting, one study showed that MRI had 79% concordance with laboratory tests for detection of persistent disease and a sensitivity of 64% for detection of remission (Bannas et al, 2012). Another study demonstrated that MRI findings of both focal and diffuse patterns correlated with treatment response, with there being an inverse correlation between the number of focal lesions observed at follow up and overall survival (Hillengass et al, 2012).

1 In other cases, MRI fails to show evidence of regression of marrow infiltration; focal  
2 lesions may shrink, remain unchanged in size (Lecouvet et al, 2001) or remain  
3 hyperintense as a result of treatment-induced necrosis and inflammation (Rahmouni  
4 et al, 1993). Furthermore, marrow changes can occur following granulocyte colony-  
5 stimulating factor (G-CSF) and erythropoietin treatment that cannot be easily  
6 distinguished from active disease (Hartman et al, 2004). In this setting, PET/CT has  
7 an advantage over MRI (see later).

8  
9 Recently, more specialised MRI techniques have been developed. Of these, whole-  
10 body diffusion weighted MRI (WB-DWI) shows great potential as a technique for  
11 assessing response to treatment. WB-DWI provides information on the difference  
12 between normal and diseased bone marrow architecture, based on differences in the  
13 motion of water at the cellular level (Messiou et al, 2011). Significant differences in  
14 measured marrow apparent diffusion coefficient (ADC) are observed between non-  
15 myeloma and myeloma patients, and between myeloma patients with active and  
16 non-active disease (Messiou et al, 2011; Hillengass et al, 2011; Messiou et al, 2012),  
17 offering a means to quantify both disease burden and response to treatment. ADC is  
18 typically higher for myeloma than normal bone marrow. An increase in ADC may be  
19 seen initially after treatment, presumably due to plasma cell death increasing  
20 extracellular space, followed by normalisation of values when normal marrow  
21 architecture is restored (Messiou et al, 2015). Whilst showing significant promise,  
22 particularly in quantifying response to treatment, further studies are warranted before  
23 WB-DWI can become fully established as a mainstream imaging tool in the  
24 management of myeloma patients.

Recommendation:

- Conventional MRI may be performed to assess response to treatment but whole-body diffusion weighted MRI (WB-DWI) should be considered where available (2C)

*Positron emission tomography/computed tomography*

FDG PET/CT, due to its ability to distinguish between active and non-active disease in myeloma, is a potentially powerful modality to assess response to treatment, predict outcome and guide treatment decisions.

Successful treatment is accompanied by a reduction or resolution of  $^{18}\text{F}$ -FDG uptake and allows for earlier evaluation as metabolic changes precede morphological changes (Caldarella C et al, 2012). Conversely, detection of increasing focal uptake of  $^{18}\text{F}$ -FDG, either in old lytic sites or in new areas is an early indicator of relapse. The usefulness of FDG PET/CT in the assessment of treatment response was confirmed in a meta-analysis of 10 studies involving 690 myeloma patients based on its ability to differentiate between metabolically active and inactive lesions (Caldarella et al, 2012). It is particularly useful for the approximately 1% of myeloma cases that are truly nonsecretory and the up to 5% of cases who have oligosecretory disease with discrepantly low intact monoclonal product or serum free light chain compared with tumour load, measured either by bone marrow biopsy or imaging. Nonsecretory and oligosecretory disease become more common with disease progression, with

1 loss of secretory capacity of some tumours at relapse (Larson *et al*, 2012). Current  
2 practice in such cases often relies on serial bone marrow biopsies, which are painful  
3 and distressing for patients. FDG-PET (Durie *et al*, 2002; Larson *et al*, 2012) and  
4 diffusion weighted MRI (Messiou and Kaiser, 2015) are particularly attractive options  
5 for monitoring nonsecretory or oligosecretory myeloma, either as a standalone  
6 measure of disease, or in conjunction with less frequent bone marrow biopsies.  
7 Furthermore, whole body imaging is less prone to anatomical sampling error than  
8 bone marrow biopsy.

9 Response assessment by FDG-PET has prognostic value with negative FDG  
10 PET/CT after treatment correlated well with improved outcome (Zamagni *et al*, 2007)  
11 including following autologous stem cell transplantation (ASCT) (Bartel *et al*, 2009;  
12 Zamagni *et al*, 2011; Lapa *et al*, 2014a). The presence/absence of minimal residual  
13 disease by flow cytometry following initial treatment is prognostic for both PFS and  
14 OS (Rawstron *et al*, 2015) and FDG-PET assessment will improve this further  
15 (Zamagni *et al*, 2015)

#### 17 Recommendation:

18 Whole body MRI/diffusion weighted MRI or FDG – PET/CT (at clinician discretion) is  
19 recommended for serial monitoring of disease burden of patients with nonsecretory  
20 myeloma, oligosecretory myeloma (1B) (which can occur at relapse in patients with  
21 previously secretory disease) and extramedullary disease (1B).

#### 23 **Use of imaging in the assessment of solitary plasmacytoma**

1 Solitary plasmacytoma is a single lesion (bone more commonly than soft tissue) that  
2 on biopsy shows infiltration by clonal plasma cells with there being no features of  
3 myeloma i.e. no CRAB (calcium elevated, renal failure, anaemia, bone lesions)  
4 features, absence of abnormal plasma cells in random sampling of bone marrow and  
5 normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary  
6 solitary lesion).

7  
8 MRI was previously recommended to assess patients with a solitary bone  
9 plasmacytoma in order to exclude other sites of disease, evidence of which would  
10 alter the diagnosis to that of multiple solitary plasmacytomas or multiple myeloma  
11 (Hughes et al, 2009; D'Sa et al, 2007) and change treatment decisions. Moulopoulos  
12 showed additional foci in a third of patients when MRI of the thoracic and  
13 lumbosacral spine was used, indicating that some patients would be under staged if  
14 an MRI was not performed (Moulopoulos et al, 1993). This was supported by  
15 Lieboss et al, who demonstrated that a skeletal survey was too insensitive to  
16 diagnose a solitary plasmacytoma (Lieboss et al 1998). However, where available,  
17 whole-body MRI should now be considered to allow more thorough assessment of  
18 disease sites elsewhere.

19  
20 Due to its ability to identify active disease in both medullary (Kannivelu et al, 2014)  
21 and extramedullary sites (Kim et al, 2014; Lapa et al, 2014b; Mulligan et al, 2011)  
22 FDG PET/CT is also a useful modality for the assessment of suspected solitary  
23 plasmacytoma (Yi et al, 2013; Lu et al. 2012). In several studies, FDG PET/CT  
24 allowed the detection of additional lesions in 30–50% of cases, which had been  
25 missed by plain X-ray or MRI of the spine (Nanni et al 2008; Salaun et al, 2008;

Schirrmeister et al, 2003). The current definition of solitary plasmacytoma requires the absence of disease outside the primary lesion by bone marrow examination and MRI (or CT) of spine and pelvis, There is thus lack of clarity both in terminology and management of those cases of solitary plasmacytoma defined according to existing criteria, but which have evidence of PET positivity. There is a lack of data on performing imaging routinely during follow up, and decisions should be guided by presence of new symptoms, or biochemical progression.

#### Recommendations:

- Either FDG PET/CT or whole body MRI should be performed to exclude additional sites of disease, and help to confirm a diagnosis of solitary plasmacytoma (1C)
- Repeat imaging should be performed when there is clinical suspicion of relapse or biochemical progression (1C)

#### Summary

Although it is clear that newer imaging techniques are replacing skeletal surveys for assessing myeloma-related bone disease in people with newly diagnosed myeloma, funding and availability for these techniques remains a barrier in most healthcare systems. The comparative effectiveness of whole-body MRI, diffusion weighted MRI, FDG PET/CT and whole-body low-dose CT is not clear. Defining patients with

1 suspected myeloma is extremely difficult, but it is clear that imaging is not necessary  
2 for patients with an obvious diagnosis of MGUS. Future research outcomes of  
3 interest are the cost effectiveness, lesion detection, sensitivity and specificity for  
4 myeloma-related bone disease, patient acceptability, incremental upstaging,  
5 radiation exposure, risk of second primary cancer, value in monitoring and the  
6 impact of additional information for predicting PFS, OS and skeletal-related events.

7  
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## 8    **Declarations of interest**

9    None of the authors had conflicts of interest to declare.

## 10   **Review process**

11   Members of the writing group will inform the writing group Chair if any new pertinent  
12   evidence becomes available that would alter the strength of the recommendations  
13   made in this document or render it obsolete. The document will be archived and  
14   removed from the BSH current guidelines website if it becomes obsolete. If new  
15   recommendations are made an addendum will be published on the BSH guidelines  
16   website. If minor changes are required due to changes in level of evidence or  
17   significant additional evidence becomes available to support current  
18   recommendations a new version of the guidance will be issued on the BSH website.

## 19   **Disclaimer**

20   While the advice and information in these guidelines is believed to be true and  
21   accurate at the time of going to press, neither the authors, the British Society for



1 Haematology nor the publishers accept any legal responsibility for the content of  
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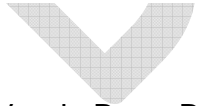
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1 **Table 1. Studies investigating MRI in the diagnostic setting with a skeletal**  
2 **survey (SS) or computed tomography (CT) as the reference standard**

3

<b>Imaging test</b>	<b>Reference standard</b>	<b>Patients</b>	<b>Whole body</b>	<b>MM stage</b>	<b>Reference</b>
MRI	SS	60	Yes	SD I-III	Dinter, et al, 2009
MRI	SS	45	Yes	SD I-III	Ghanem et al, 2006
MRI	SS	611	No	SD II-III	Walker et al, 2007
MRI	SS	77	No	SD I-III	Baur et al, 2002
MRI	SS	18	No	SD I-III	Mahnken et al, 2002
MRI	SS	80	No	SD I-III	Lecouvet et al, 1999
MRI	SS	55	No	SD I	Mariette et al, 1999
MRI	SS	23	No	SD I	Dimopoulos et al, 1993



MRI	CT	41	Yes	SD I-III	Baur-Melnyk et al, 2008
MRI	CT	48	No	SD I-III	Laroche et al, 1996

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DRAFT

Table 2 Recommendations for myeloma imaging and reporting using PET/CT \*

Whole body imaging should be performed from vertex to toes, if tolerated, using European guidelines for tumour imaging with FDG 60 m post-FDG administration [Boellaard et al 2015]

The following should be reported :

1. **Number of Focal** lesions (FL) with increased FDG uptake ( > 3 FL shown to be prognostic at diagnosis and during treatment) and **distribution and standardised uptake values (SUV)max as appropriate**

Note MM lesions may have focal uptake with no CT abnormality, osteolytic change or soft tissue density within marrow spaces

2. Presence of **associated CT findings** e.g. osteolytic lesions, osteoblastic lesions, acute and chronic fractures, pathological fractures
3. Presence of **extramedullary disease**  
to be differentiated from 'break-out lesions' where the lesion involves bone with cortical disruption and soft tissue extension. Size of soft tissue mass/es may be helpful.
4. Risk of cord compression or invasion of base of skull
5. Presence of diffuse bone marrow uptake > liver
6. Sites for possible biopsy if appropriate
7. Other relevant findings such as infection- or disease-related complications e.g. avascular necrosis, osteonecrosis
8. Previous surgical interventions e.g. vertebroplasty, prostheses and orthopaedic devices

1 \*Modified from Mesguich et al European Journal of Radiology 2014; 83: 2203-2223

1

2 Table 3 Interpretation of FDG bone and bone marrow uptake in patients with  
 3 myeloma \* (given the limited evidence it is not possible to give a consensus on  
 4 the interpretation of extramedullary disease)

Patterns of uptake	Pre treatment	Post treatment	Other causes of 'false positive' FDG uptake
Focal bone uptake	<p>Positive:</p> <p>Intensity &gt; uptake in normal bone marrow and/or normal liver with or without lytic changes on CT (although lytic changes needed for IMWG definition**)</p> <p>Negative:</p> <p>Uptake that corresponds to another cause of FDG uptake e.g. degenerative joint disease</p>	<p>Positive: intensity &gt; normal liver with stable or new lytic lesion or without CT abnormality [Note for local RT treatment increased uptake may occur due to inflammation if scanned within 3 months of treatment]</p> <p>Negative: intensity &lt; normal liver</p> <p>Equivocal: FDG uptake associated</p>	<p>Trauma</p> <p>Osteoporotic fracture (especially vertebral body, ribs, sacrum)</p> <p>Stress fracture, Bone infarcts (especially femoral head)</p> <p>Degenerative joint disease</p> <p>Orthopaedic devices and surgical interventions</p>

	<p>Equivocal:</p> <p>Uptake corresponding to rib fracture or bone lesions with sclerotic change on CT</p>	<p>with previous lytic lesion with development of sclerosis could represent treatment response</p>	
<p>Diffuse bone marrow uptake</p>	<p>Positive:</p> <p>intensity &gt; normal liver</p> <p>but reactive changes can give similar appearances</p> <p><i>Correlation with MRI or bone marrow biopsy advised as appropriate</i></p> <p>Negative:</p> <p>Intensity <math>\leq</math> normal liver</p>	<p>Positive:</p> <p>Heterogeneous uptake &gt; normal liver</p> <p>Equivocal:</p> <p>Homogenous uptake should be correlated with MRI and laboratory data</p>	<p>Bone marrow colony stimulation (though not commonly used in MM)</p>

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2 \*Modified from Mesguich et al European Journal of Radiology 2014; 83: 2203-2223

3 \*\*The revised IMWG definition (Rajkumar et al, 2014) states that increased uptake

4 on PET-CT alone is not adequate evidence for the diagnosis of a bone lesion due to

1 multiple myeloma; evidence of underlying osteolytic bone destruction is needed on  
2 the CT portion of the examination.

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4 Abbreviations:

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DRAFT